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Use of the 6-Min Walk Distance to Identify Variations in Treatment Benefits From Implantable Cardioverter-Defibrillator and Amiodarone

Results From the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial)

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Objectives The purpose of this study was to determine if 6-min walk test data assists in treatment decisions for patients with heart failure.

Background In the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), a pre-specified subgroup analysis showed that patients with New York Heart Association functional class III symptoms did not benefit from implantable cardioverter-defibrillator (ICD) therapy and appeared to be harmed by amiodarone, whereas New York Heart Association functional class II patients obtained significant survival benefit from ICD. We postulated that a more objective measure of functional capacity, such as 6-min walk (6MW) distance, might provide a better tool for selecting these preventive therapies.

Methods A 6MW test was performed before randomization in 2,397 patients. Median follow-up was 45.5 months. All-cause mortality was the primary endpoint, with cause-specific mortality (heart failure, arrhythmic) examined in secondary analyses.

Results The hazard ratios (HRs) for ICD therapy compared to placebo were estimated within tertiles of baseline 6MW distance: HR: 0.42 (95% confidence interval [CI]: 0.26 to 0.66) for 6MW distance >386 m (top tertile); HR: 0.57 (95% CI: 0.39 to 0.83) for 6MW distance 288 to 386 m (middle tertile); and HR: 1.02 (95% CI: 0.75 to 1.39) for 6MW distance <288 m (bottom tertile). The corresponding HRs for amiodarone compared to placebo were 0.68 (95% CI: 0.46 to 1.02) for the top, 0.86 (95% CI: 0.61 to 1.21) for the middle, and 1.56 (95% CI: 1.17 to 2.09) for the bottom tertile. The 6MW distance was inversely related to heart failure–related mortality but not to arrhythmic mortality. ICD therapy reduced arrhythmic mortality in the top 2 tertiles of 6MW, but had no effect on heart failure mortality.

Conclusions A baseline 6MW distance <288 m identified a subgroup of SCD-HeFT patients who were harmed by amiodarone therapy and did not benefit from ICD. (Sudden Cardiac Death in Heart Failure Trial [SCD-HeFT]; NCT00000609) (J Am Coll Cardiol 2014;63:2560–8) © 2014 by the American College of Cardiology Foundation

The SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) found that conservatively programmed, single-lead implantable cardioverter-defibrillator (ICD) therapy reduced all-cause mortality relative to standard medical therapy in patients with New York Heart Association (NYHA) functional class II or III heart failure and a left ventricular

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ejection fraction (LVEF) ≤35% (1). An unanticipated finding of the trial was that patients with NYHA functional class II heart failure had a 46% reduction in mortality with ICD therapy, but patients with NYHA functional class III heart failure did not appear to benefit from ICD therapy and trended toward harm. In addition, NYHA functional class II patients obtained no benefit from amiodarone, whereas class III patients had a statistically significant increase in mortality compared with patients in the placebo group.

NYHA functional classification is a widely used and well accepted measure of functional capacity that has only fair interobserver reproducibility (2). Nevertheless, it has the advantage of wide familiarity, easy application, demonstrated prognostic importance, and no cost. The 6-min walk (6MW) test shares many of those qualities but adds the additional advantage of being a more structured, objective measure of functional capacity (3). Prior investigations have shown that distance walked during the 6MW test correlates moderately with NYHA functional class, peak oxygen consumption, and assessments of quality of life (4–6). Additionally, 6MW distance has been found to predict mortality and hospital stay in heart failure patients (7–9). We postulated that if the differences observed in therapeutic benefit in SCD-HeFT from amiodarone or ICD therapy according to NYHA functional class were robust, they would also be evident using the 6-min walk test.

Methods

Design and primary clinical results of SCD-HeFT. The design of SCD-HeFT has been described previously (1,10). In brief, 2,521 patients with stable NYHA functional class II or III heart failure due to ischemic and nonischemic cardiomyopathy and an LVEF ≤35% were randomized to receive placebo, amiodarone, or a single-lead ICD programmed to shock-only mode with pacing only for extreme bradycardia. Study protocol approval was obtained from each site's institutional review board or ethics committee. Randomization was stratified by the presence of coronary disease and NYHA functional class II or III. NYHA functional class was assigned by the investigator at enrollment. NYHA functional class I and IV patients were excluded. Investigators were encouraged to treat study patients with optimal medical therapy, including an angiotensin-converting enzyme inhibitor and a beta-blocker as well as spironolactone, aspirin, and a statin if appropriate. The primary endpoint of the trial was death from any cause. Informed consent was obtained from all patients. Patients were enrolled at 148 sites in the United States, Canada, and New Zealand from September 16, 1997, to July 18, 2001. All patients were followed until October 31, 2003. Vital status was known at the end of the trial for 100% of patients enrolled. Treatment assignment was balanced, with 847 patients assigned to placebo, 845 to amiodarone, and 829 to ICD therapy. No significant differences in overall baseline demographic or clinical characteristics were found among the 3 treatment groups (1).

SCD-HeFT demonstrated that in patients with NYHA functional class II or III heart failure and an LVEF ≤35%, conservatively programmed, single-lead ICD therapy improved survival (hazard ratio [HR]: 0.77; 97.5% confidence interval [CI]: 0.62 to 0.96; p = 0.007) (1). The trial also found no survival benefit from amiodarone (HR: 1.06; 97.5% CI: 0.86 to 1.30; p = 0.53) compared with placebo in this cohort. Further, in prespecified subgroup analyses, patients with NYHA functional class III symptoms at baseline did not benefit from ICD therapy (HR: 1.16; 97.5% CI: 0.84 to 1.61; p = 0.30) and were harmed by amiodarone (HR: 1.44; 97.5% CI: 1.05 to 1.97; p = 0.010).

Abbreviations and Acronyms

CI = confidence interval
HR = hazard ratio
ICD = implantable cardioverter-defibrillator
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
6MW = 6-min walk

6MW test. A 6MW test was performed after consent was obtained prior to randomization. Investigators were given detailed guidelines for performance of the 6MW test (10), which was modified from that described by Guyatt et al. (3). A 60-foot (18.3 m) course in an enclosed corridor was marked, and a chair was placed at each end. Patients were asked to walk at their own pace from chair-to-chair, but were instructed to cover as much distance as possible during the allotted 6 min. Patients were allowed to stop and rest during the test but were instructed to resume walking as soon as they were able. Standardized verbal encouragement was provided every 30 s. Coaching or enthusiastic urging were prohibited. After 6 min, patients were instructed to stop walking, and the distance covered was recorded. Symptoms of dyspnea, angina, and/or lightheadedness experienced by the patient during the walk test were also recorded. The results were measured in feet and converted to meters in the analysis to permit easier comparison with prior data.

Data analysis. Medians with interquartile ranges were used to describe continuous variables. Frequencies and percents were used to describe categorical variables. To facilitate descriptive analyses as well as illustration of multivariable modeling results, 6MW distances were divided into tertiles, with dividing points at 288 and 386 m. Baseline characteristics were compared among tertiles using the Jonckheere-Terpstra test (11) for continuous variables and the Mantel-Haenszel chi-square test for categorical variables. Incidence of symptom types was also compared among tertiles using the Mantel-Haenszel chi-square test (11).

Mortality curves were generated using Kaplan-Meier methods (12). Treating 6MW distance as a continuous variable, Cox proportional hazards models were used to assess the relationship of 6MW distance to mortality (13). Restricted cubic splines were used to determine whether the relationship as characterized with the Cox model was strictly linear (14). Interactions between 6MW distance and randomized

treatment were tested within the model to determine whether the effect of ICD or amiodarone (vs. placebo) varied with 6MW distance. Because these interactions were significant, the relationship of 6MW distance to mortality risk was estimated within treatment groups separately. Similarly, ICD and amiodarone HRs (vs. placebo) were estimated using subgroup models within 6MW tertiles. Comparisons of amiodarone and ICD with placebo were performed according to the intention-to-treat principle. All Cox models included baseline covariates previously identified as predictors of mortality in SCD-HeFT: age, sex, heart failure etiology (ischemic vs. nonischemic), NYHA functional class, LVEF, time since heart failure diagnosis, diabetes, mitral regurgitation, substance abuse, renal insufficiency, systolic blood pressure, PR interval, corrected QT interval, intraventricular conduction delay, and use of an angiotensin-converting enzyme inhibitor or digoxin. Risk relationships are expressed as HRs with associated 95% CIs. To compare the predictive value of NYHA functional class and 6MW distance, we calculated the incremental model likelihood ratio chi-square statistics and c-statistics (model with and without variable of interest but containing all other adjustment variables listed above). These provide a measure of the "prognostic information content" of each variable after adjustment for other relevant baseline prognostic factors.

A clinical events committee that was blinded to the patients' treatment assignment classified the cause of death (15).

Results

Study population baseline characteristics. A total of 2,397 (95.1%) SCD-HeFT patients performed a baseline 6MW test; 117 patients were unable to perform the test, and data were missing on 7 patients. There were significant differences in baseline characteristics among tertiles of 6MW distance (Table 1). Shorter 6MW distance was associated with a higher prevalence of older age, female sex, nonwhite race, lower weight, NYHA functional class III, ischemic heart failure etiology, history of diabetes, history of hypertension, and history of pulmonary disease. There were no significant associations with standard predictors of heart failure severity including LVEF, systolic blood pressure, or serum sodium. Biomarkers, such as brain type natriuretic peptides, were not assessed during the study.

The median 6MW distance for the entire study group was 342 m (25th, 75th percentiles: 255, 412 m). The distribution of 6MW distance within treatment groups was nearly identical (Table 2). Patients who walked shorter distances were more likely to be symptomatic during the test, with dyspnea as the predominant symptom reported (Table 3).

Table 1 Baseline Characteristics by 6MW Distance Tertile

	6MW Distance, m			
	<288 (n = 787)	288–386 (n = 809)	>386 (n = 801)	p Value
Randomized treatment				0.32
ICD	34% (270)	32% (262)	32% (256)	
Amiodarone	33% (261)	34% (273)	34% (275)	
Placebo	33% (256)	34% (274)	34% (270)	
Age, yrs	64 (55, 71)	59 (51, 68)	57 (49, 65)	<0.0001
Female	32% (254)	25% (202)	13% (104)	<0.0001
Nonwhite race	31% (246)	23% (184)	16% (131)	<0.0001
Weight, lbs	184 (159, 214)	189 (161, 221)	195 (169, 222)	<0.0001
NYHA functional class III	50% (395)	25% (201)	12% (96)	<0.0001
Ischemic HF etiology	57% (446)	51% (416)	46% (367)	<0.0001
Ejection fraction, %	25 (20, 30)	25 (20, 30)	24 (20, 30)	0.90
Systolic blood pressure, mm Hg	118 (106, 130)	120 (107, 132)	117 (104, 130)	0.14
Serum sodium, mEq/l	139 (137, 141)	139 (137, 141)	139 (137, 141)	0.67
Serum creatinine, mg/dl	1.2 (1.0, 1.4)	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	<0.0001
Diabetes	37% (295)	30% (244)	22% (173)	<0.0001
Hypertension	63% (496)	56% (449)	46% (372)	<0.0001
Current smoker	18% (142)	17% (135)	14% (111)	0.024
Pulmonary disease	25% (193)	19% (151)	13% (103)	<0.0001
Atrial fibrillation/flutter	18% (139)	14% (111)	13% (106)	0.013
Prior MI	73% (376)	72% (364)	69% (311)	0.21
Prior stroke	10% (75)	6% (49)	3% (22)	<0.0001
ACE-I or ARB	95% (744)	97% (788)	98% (784)	0.0002
Beta-blocker	64% (501)	71% (571)	73% (584)	<0.0001

Values are % (n) or median (25th, 75th percentiles). Race was self-reported on the clinical case report form.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; HF = heart failure; ICD = implantable cardioverter-defibrillator; MI = myocardial infarction; NYHA = New York Heart Association; 6MW = 6-min walk.

Table 2 6MW Distance by Treatment Group, HF Etiology, and NYHA Functional Class

	All Patients (N = 2,521)	Amiodarone (n = 845)	Placebo (n = 847)	ICD Therapy (n = 829)	Ischemic (n = 1,310)	Nonischemic (n = 1,211)	NYHA Functional Class II (n = 1,761)	NYHA Functional Class III (n = 760)
Walk distance								
Feet	1,130 (840–1,360)	1,136 (840–1,373)	1,136 (850–1,374)	1,123 (840–1,348)	1,095 (780–1,320)	1,163 (899–1,405)	1,200 (966–1,435)	894 (600–1,137)
Meters	342 (255–412)	344 (255–416)	344 (258–416)	340 (255–408)	332 (236–400)	352 (272–426)	364 (293–435)	271 (182– 344)
<288 m	31% (787)	31% (261)	30% (256)	33% (270)	34% (446)	28% (341)	22% (392)	52% (395)
288–386 m	32% (809)	32% (273)	32% (274)	32% (262)	32% (416)	32% (393)	35% (608)	26% (201)
>386 m	32% (801)	33% (275)	32% (270)	31% (256)	28% (367)	36% (434)	40% (705)	13% (96)
Unable to walk	5% (117)	4% (35)	5% (45)	5% (37)	6% (77)	3% (40)	3% (51)	9% (66)
Missing data	0.3% (7)	0.1% (1)	0.2% (2)	0.5% (4)	0.3% (4)	0.3% (3)	0.3% (5)	0.3% (2)
Symptomatic	62% (1,491)	61% (497)	62% (493)	64% (501)	63% (777)	61% (714)	54% (925)	82% (566)

Values are median (interquartile range) and % (frequency). Percent for symptomatic status is among patients completing the 6MW distance test.
Abbreviations as in Table 1.

6MW distance and all-cause mortality. PRELIMINARY MODEL CHECKING. There were significant interactions between 6MW distance and treatment (ICD or placebo [p = 0.0006], amiodarone or placebo [p = 0.0004]), indicating that the association of 6MW distance with mortality risk varied by treatment group and the effect of treatment varied according to 6MW distance. Subsequent modeling was done either in treatment subgroups or 6MW distance tertile subgroups, according to the question being evaluated. Within each treatment group, the relationship of 6MW distance to mortality risk as characterized by the log hazard ratio in the Cox model was linear (all p > 0.7 for nonlinearity tests), indicating that there was no 6MW distance below which mortality increased at a substantially accelerated rate.

6MW DISTANCE AND MORTALITY (ASSESSED IN TREATMENT SUBGROUPS). In patients assigned to placebo, there were 60 deaths (3-year Kaplan-Meier rate: 17.8%) in the highest 6MW distance tertile, 78 deaths (21.6%) in the middle tertile, and 83 deaths (24.7%) in the lowest tertile (Fig. 1). In patients assigned to amiodarone, there were 45 deaths (14.2%) in the highest 6MW distance tertile, 63 deaths (16.6%) in the middle tertile, and 115 deaths (38.7%) in the lowest tertile. In patients assigned to ICD therapy, there were 28 deaths (7.0%) in the highest 6MW distance tertile, 44 deaths (12.4%) in the middle tertile, and 92 deaths (28.0%) in the lowest tertile.

For placebo patients, the unadjusted HR for each 50-m increase in 6MW distance was 0.93 (95% CI: 0.88 to 0.98; p = 0.0069). The corresponding adjusted HR was 1.00 (95% CI: 0.93 to 1.06; p = 0.89). Among patients randomized to amiodarone, the unadjusted HR was 0.80 (95% CI: 0.76 to 0.85; p < 0.0001) and the adjusted HR was 0.90 (95% CI: 0.84 to 0.96; p = 0.0019) for each 50-m increase in 6MW distance. For ICD patients, the unadjusted HR was 0.77 (95% CI: 0.73 to 0.83; p < 0.0001) and the adjusted HR was 0.88 (95% CI: 0.81 to 0.96; p = 0.0025) for each 50-m increase in 6MW distance.

6MW DISTANCE AND TREATMENT BENEFIT (ASSESSED IN 6MW DISTANCE TERTILES). ICD therapy significantly reduced mortality in the top and middle tertiles of 6MW distance versus placebo (HR: 0.42 [95% CI: 0.26 to 0.66], p = 0.0002 in the highest tertile and HR: 0.57 [95% CI: 0.39 to 0.83], p = 0.0035 in the middle tertile) but was neutral in patients with the lowest 6MW distances (HR: 1.02 [95% CI: 0.75 to 1.39], p = 0.90 in the lowest tertile) (Fig. 2, Table 4). For amiodarone relative to placebo, in the lowest 6MW distance tertile, amiodarone increased mortality (HR: 1.56 [95% CI: 1.17 to 2.09], p = 0.0028). In the middle tertile, amiodarone had a relatively neutral effect on mortality (HR: 0.86 [95% CI: 0.61 to 1.21], p = 0.38). In the highest tertile, there was a marginal trend toward survival benefit with amiodarone (HR: 0.68 [95% CI: 0.46 to 1.02], p = 0.061).

6MW distance and cause-specific mortality. 6MW DISTANCE AND HEART FAILURE MORTALITY. When the relationship

Table 3 Symptoms During Baseline 6-Min Walk by Distance Tertile

	<288 m (n = 787)	288–386 m (n = 809)	>386 m (n = 801)	p Value
Asymptomatic	25% (196)	39% (312)	50% (398)	<0.0001
Symptomatic	75% (591)	61% (497)	50% (403)	
Dyspnea	62% (490)	51% (413)	43% (344)	<0.0001
Lightheadedness	12% (97)	8% (67)	4% (33)	<0.0001
Angina	6% (46)	6% (46)	3% (28)	0.031
Near syncope	0.4% (3)	0	0	—
Syncope	0	0	0	—
Other	38% (298)	28% (227)	18% (141)	<0.0001

between 6MW distance and heart failure deaths was examined (censoring all other causes of death), an inverse prognostic gradient of effect was seen for all 3 treatment arms in the unadjusted data (Fig. 3), with lower 6MW distance results associated with higher mortality. Unadjusted HR for a 50-m increase in 6MW distance: 0.79 for ICD, 0.81 for amiodarone, and 0.87 for placebo (all $p < 0.006$). After adjustment, the prognostic gradient for 6MW distance was reduced in magnitude and was no longer statistically significant: the HR for 50-m increase in 6MW distance was 0.91 for ICD ($p = 0.14$), 0.94 for amiodarone ($p = 0.36$), and 0.94 for placebo ($p = 0.37$).

Comparing treatments within 6MW distance tertiles after adjustment and censoring all non–heart failure deaths, the HR for ICD relative to placebo was 0.73 (95% CI: 0.32 to 1.64) in the top 6MW distance tertile, 0.66 (95% CI: 0.34 to 1.30) in the middle 6MW distance tertile, and 1.22 (95% CI: 0.73 to 2.03) in the bottom 6MW distance tertile. For amiodarone, the corresponding HRs were 0.94 (95% CI: 0.41 to 2.19), 1.10 (95% CI: 0.60 to 2.01), and 1.20 (95% CI: 0.70 to 2.05).

6MW DISTANCE AND ARRHYTHMIC MORTALITY. The unadjusted relationship between 6MW distance and risk of arrhythmic deaths (censoring all other causes of death) varied by treatment group (Fig. 4): the HR for a 50-m increase in 6MW distance was 0.73 for ICD ($p < 0.0001$), 0.95 for amiodarone ($p = 0.30$), and 1.05 for placebo ($p = 0.30$). After adjustment, the HR for 50-m increase in 6MW distance was 0.85 in the ICD arm ($p = 0.13$), 1.04 in the amiodarone arm ($p = 0.56$), and 1.13 in the placebo arm ($p = 0.022$).

Comparing treatments within 6MW distance tertiles after adjustment and censoring all nonarrhythmic deaths, the HR for ICD relative to placebo was 0.10 (95% CI: 0.03 to 0.33) ($p = 0.0002$) in the top 6MW distance tertile, 0.36 (95% CI: 0.17 to 0.75) ($p = 0.007$) in the middle 6MW distance tertile, and 0.72 (95% CI: 0.38 to 1.35) ($p = 0.31$) in the bottom 6MW distance tertile. The corresponding HRs for amiodarone versus placebo were 0.62 (95% CI: 0.35 to 1.12) ($p = 0.11$), 0.78 (95% CI: 0.44 to 1.38) ($p = 0.39$), and 1.06 (95% CI: 0.59 to 1.89) ($p = 0.86$).

Prognostic value of 6MW distance versus NYHA functional class. Adjusting for baseline clinical and demographic variables but excluding NYHA functional class and 6MW distance, the model LR chi-square value was 360.8 and c-statistic was 0.702 (Online Table 1). After adding NYHA functional class, the value increased to 413.4 (incremental chi-square 52.6) and c-statistic increased to 0.716. After adding 6MW distance (and with NYHA functional class excluded), the value increased to 423.7 (incremental chi-square 62.9) and the c-statistic increased to 0.722.

One of the unexpected findings of the present investigation was that 6MW distance was not an independent predictor of all-cause mortality in the placebo patients (adjusted HR: 1.0 for 50 m increase in 6MW distance, $p = 0.89$) but was an independent prognostic factor in the ICD (adjusted HR: 0.88, $p = 0.0025$) and the amiodarone (adjusted HR: 0.90, $p = 0.0019$) patients. To understand these results, we did additional exploratory analyses using cause-specific mortality analyses (heart failure, and arrhythmic, with all other deaths censored) within each treatment group. We found that the 6MW distance had a clear inverse gradient with heart failure mortality (lowest 6MW distance associated with highest mortality rate) that was almost identical in the 3 treatment groups (Fig. 3) (unadjusted HRs: 0.87 for ICD, 0.88 for amiodarone, and 0.92 for placebo; all $p < 0.001$). After adjustment, the prognostic gradient with heart failure mortality was lost for all 3 treatment groups (HRs: 0.94 for ICD, 0.97 for amiodarone, and 0.96 for placebo; all $p > 0.10$). The patterns were more complex when we examined 6MW distance against arrhythmic death, censoring other modes of death. In the unadjusted data (Fig. 4), there was again an inverse gradient of mortality with 6MW distance for ICD and amiodarone, but the relationship in the placebo arm was flat in the lowest and middle tertiles with a modest increase in the mortality risk in the highest tertile. Whether this latter effect is a chance variation in the data or a reproducible feature of the prognostic information conveyed by the 6MW test cannot be determined from our data. One additional aspect of note is that, although the unadjusted patterns of arrhythmic mortality versus 6MW distance for ICD and amiodarone-treatment

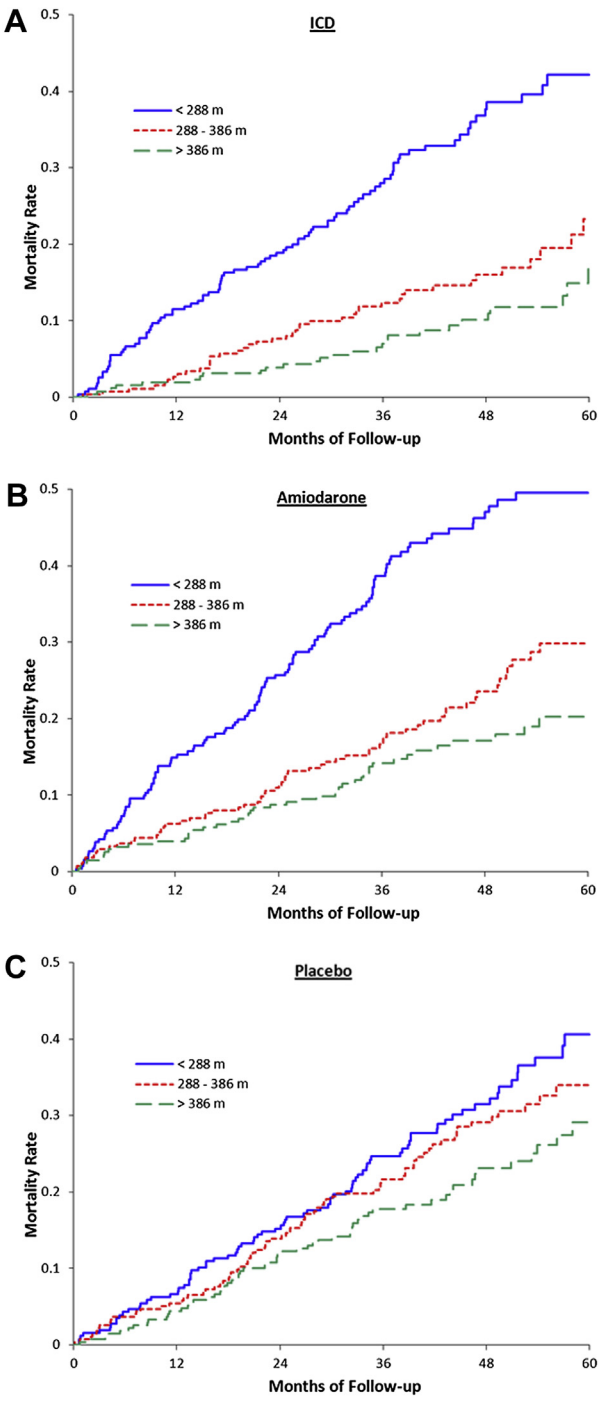

Figure 1 6-Min Walk Distance and Mortality in Treatment Subgroups

Kaplan-Meier estimates of death from any cause by 6-min walk tertile and stratified by treatment group. The data are unadjusted. ICD = implantable cardioverter-defibrillator.

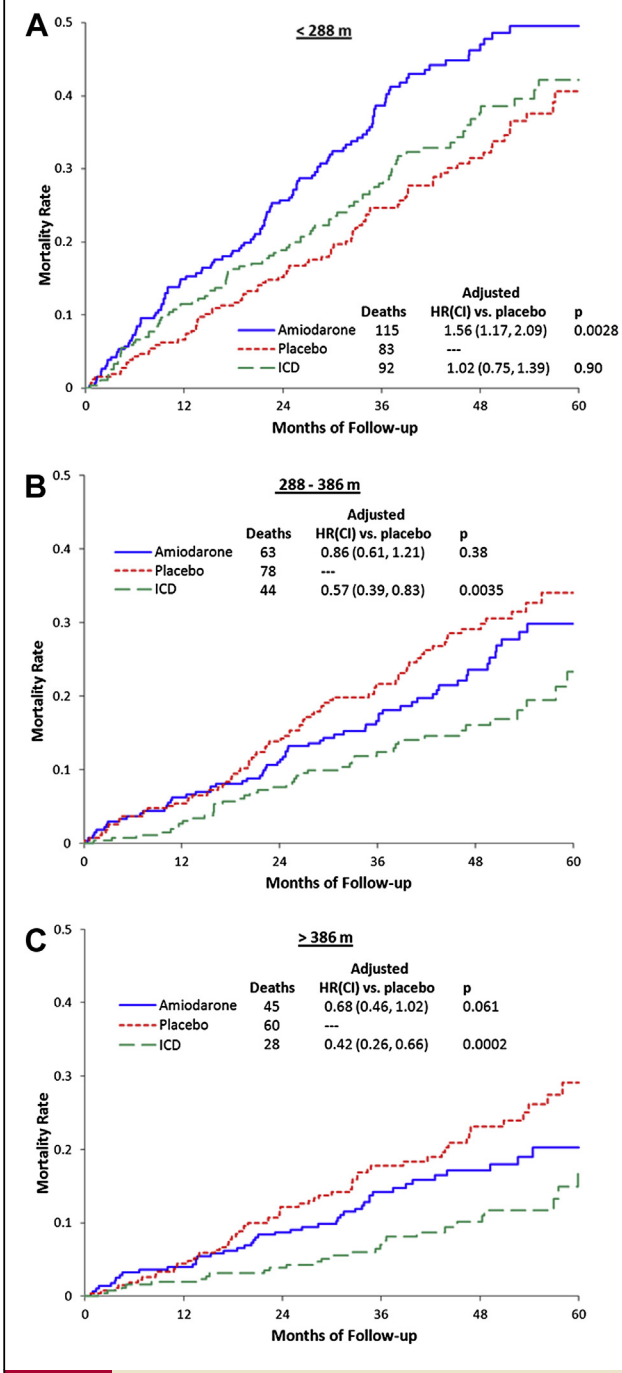

Figure 2 Treatment Effects on Mortality in 6-Min Walk Distance Subgroups

Kaplan-Meier estimates of death from any cause, by treatment group stratified by 6-min walk distance tertile. CI = confidence interval; HR = hazard ratio; ICD = implantable cardioverter-defibrillator.

groups had the same general slope, the amiodarone absolute mortality was shifted up for every level of 6MW distance relative to the ICD arm (about 3 per 100 more arrhythmic deaths in the lowest 6MW tertile, 2 per 100 in the middle tertile, and almost 5 per 100 in the top tertile). After adjustment, the prognostic relationship of 6MW distance became largely flat across the tertiles for ICD and amiodarone and showed a trend toward increased mortality in the

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Table 4 Mortality Rates and HRs for Randomized Treatments, by 6MW Distance Tertile

	3-yr KM Mortality Rate			ICD vs. Placebo		Amiodarone vs. Placebo	
6MW Distance, m	ICD	Amiodarone	Placebo	HR (95% CI)	p Value	HR (95% CI)	p Value
<288	28.0	38.7	24.7	1.02 (0.75–1.39)	0.90	1.56 (1.17–2.09)	0.0028
288–386	12.4	16.6	21.6	0.57 (0.39–0.83)	0.0035	0.86 (0.61–1.21)	0.38
>386	7.0	14.2	17.8	0.42 (0.26–0.66)	0.0002	0.68 (0.46–1.02)	0.061

CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; other abbreviations as in Table 1.

placebo arm (HR: 1.08 for each 50-m increase in 6MW distance, p = 0.02).

Discussion

This study confirms and extends previous findings from the SCD-HeFT trial showing that the survival benefit of primary prevention ICD therapy varies importantly depending upon baseline functional capacity. The original report from the trial showed that, in pre-specified subgroup testing, NYHA functional class III patients did not benefit from ICD therapy, whereas NYHA functional class II patients derived a large survival benefit. Implementation of these findings in practice and incorporation into clinical guidelines has been resisted, however, in part because of concerns about the subjective nature of the NYHA functional class. The major objective of the present investigation, therefore, was to evaluate whether the 6MW test, which is generally viewed as a more objective and reliable means of assessing functional capacity in heart failure patients, was also able to identify variations in treatment benefits of ICD therapy similar to what was previously shown with NYHA functional class. We found that patients with more advanced heart failure, as reflected by a 6MW distance <288 m (lower tertile), did not benefit from ICD therapy, whereas those with 6MW distances >288 m (middle and upper tertiles) benefited substantially. Supplementary analyses looking at mode of death as classified by the SCD-HeFT blinded clinical events committee showed, as expected, that single-lead ICD therapy had no benefit on heart failure deaths regardless of 6MW distance; however, it substantially and significantly lowered arrhythmic mortality in the top 2 tertiles of 6MW distance, but not for patients with a 6MW distance <288 m.

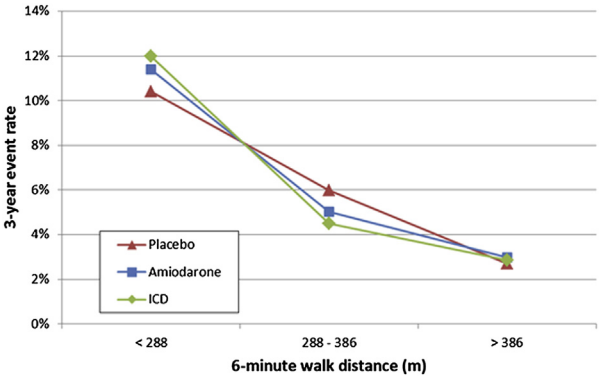

Figure 3 6-Min Walk Distance and Heart Failure Mortality

Kaplan-Meier estimates of 3-year rate of death from heart failure with all other causes of death censored. Data are unadjusted, and the x-axis shows tertiles of 6-min walk distance. ICD = implantable cardioverter-defibrillator.

Of note, only about one-half of the SCD-HeFT patients in NYHA functional class III had a 6MW distance <288m, and 13% were actually in the highest 6MW distance tertile (>386 m) (Table 2). Conversely, only 50% of the patients with a 6MW distance <288 m were in NYHA functional class III. Thus, NYHA functional class III and 6MW test distance <288 m do not identify the same patient subgroups. Judged on the basis of the amount of incremental prognostic information provided, 6MW distance was modestly more powerful than NYHA functional class (Online Table 1). More prognostic information, as measured in this way, however, does not necessarily equate to better clinical treatment selection. At the individual patient level, clinicians must therefore continue to exercise judgment as to the suitability of advanced heart failure patients for primary prevention ICD therapy, recognizing that sicker patients are much less likely to benefit. Judgment as to when the patient is "too sick to benefit" can reasonably take into account both the NYHA functional class and the 6MW distance. Establishing which treatment decision rule (i.e., on the basis of NYHA functional class or on 6MW distance) more often leads to better survival at the population level cannot be determined from the SCD-HeFT study data. Another approach to treatment selection involves the use of multivariable statistical prediction models that can account for the relative importance and inter-relationships of many more variables in predicting outcome, such as the Seattle Heart Failure Model (16). Using this model, Levy et al. (16) divided the SCD-HeFT group into quintiles on the basis of predicted risk for all-cause mortality and found that ICD therapy provided enhanced survival for the bottom 4 quintiles. The top quintile (highest-risk group), which derived no benefit from ICD therapy, resembled the subgroup of patients with 6MW distance <288 m in this analysis, with a 6MW median distance of 280 m, and 61% with NYHA functional class III.

Our findings on amiodarone therapy for primary prevention are also consistent with the original SCD-HeFT

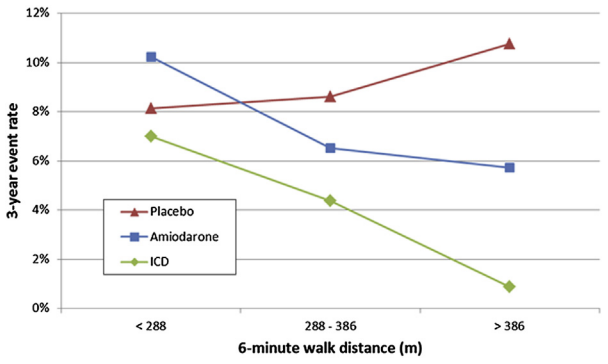

Figure 4 6-Min Walk Distance and Arrhythmic Mortality

Kaplan-Meier estimates of 3-year rate of death from arrhythmic cause with all other causes of death censored. Data are unadjusted. The x-axis shows tertiles of 6-min walk distance. ICD = implantable cardioverter-defibrillator.

report, which found a 44% increase in mortality for NYHA functional class III patients randomized to amiodarone ($p = 0.01$) (1). In the present analysis, patients with a 6MW distance <288 m had a 56% increase in mortality with amiodarone ($p = 0.003$). In the supplemental analyses of cause-specific mortality for patients with a 6MW distance <288 m, the HR indicated a trend toward increased heart failure mortality with amiodarone but with wide confidence limits. In the analysis of arrhythmic deaths, amiodarone had a neutral effect in patients with a 6MW distance <288 m (HR: 1.06, $p = 0.86$). Thus, the reason for the adverse results for amiodarone therapy in the patients with more severe heart failure remains unclear, but the present analysis at least suggests that this finding was not dependent on NYHA functional class. It is also possible that amiodarone increases the risk of bradycardia or ventricular conduction delays in patients with more advanced heart failure and significant conduction system disease. The findings in the dronedarone trial were similar and may indicate a class effect (17). At minimum, these results suggest that restraint in using amiodarone would be prudent in more vulnerable patients. It is important to recognize, however, that amiodarone was used in this trial for primary prevention and not in patients with atrial and ventricular arrhythmias.

Taken together, these results suggest the following points. First, the unadjusted data for both the ICD and amiodarone arms showed the expected inverse gradient between SWM distance and mortality, and patterns consistent with this were seen for both heart failure and arrhythmic deaths. The difference in all-cause mortality rates between the lowest and highest 6MW distance tertiles was about 28 per 100 for amiodarone and 23 per 100 for ICD patients. Second, the placebo pattern was more complex, because the inverse gradient of heart failure deaths with 6MW distance (shorter distance, higher death rate) was partially cancelled out by an increase in arrhythmic deaths in the top tertile of 6MW distance, leaving a net modest prognostic 10 per 100 difference in all-cause mortality between the lowest and highest 6MW tertiles. Third, after multivariable adjustment, the 6MW distance did not retain any independent prognostic information in the placebo arm due to the smaller absolute differences between the low- and high-risk groups, which presumably reflect the underlying discordant relationships in cause-specific mortality described in the previous text.

An inverse relationship between 6MW distance and mortality was demonstrated in a sub-study of 898 patients from the SOLVD (Studies of Left Ventricular Dysfunction), in which low 6MW distance predicted higher mortality and hospital stay (7). An analysis of 6MW distance in 331 patients from the FIRST (Flolan International Randomized Survival Trial) (a trial examining survival in women with moderate to severe heart failure) also demonstrated an association between low 6MW distance and mortality (8). Interestingly, 6MW distance was a more powerful predictor of death in each of these studies than in the placebo group in SCD-HeFT, but this may be because SCD-HeFT patients received more prognosis-modifying medical therapy. Patients in the SOLVD and FIRST trials were not treated with beta-blockers. The placebo group in SCD-HeFT had a 7.2% annual mortality (compared to an annual mortality of 12% in SOLVD and a 6-month mortality of approximately 26% in FIRST in both men and women). The SOLVD group more readily matches the SCD-HeFT group. Mancini et al. (18,19) had similar findings regarding predictors and their power in the presence of beta-blockade. Using peak oxygen consumption rather than 6MW distance, Mancini et al. (18,19) found it to be a significantly less powerful predictor of mortality in patients on beta-blockers than in patients not treated with beta-blockers. It is to be expected that risk predictors lose power in study groups at lower risk.

This study is notable for being the largest evaluation of the relationship between 6MW distance and survival in heart failure patients receiving evidence-based medical therapy. It is also the first to examine the benefit of primary prevention ICD and amiodarone therapy according to 6MW distance.

Study limitations. Finally, some caveats should be considered in the interpretation of our findings. First, the use of a single variable, either NYHA functional class or 6MW distance, to identify patients who may not benefit from an ICD and who may be at a particularly increased risk from amiodarone therapy will never be as accurate or precise as a method based on a fuller accounting of patient risk using multivariable models. However, as long as physicians continue to use simpler decision rules in practice, it will be important to have an understanding of the key drivers of treatment benefit and their limitations. Second, patients with more advanced heart failure, such as those in NYHA functional class III or with a 6MW distance <288 m, may be candidates for cardiac resynchronization therapy, and

such therapy often includes ICD functioning. Because CRT therapy has the potential to improve the heart failure state, our findings about the benefit of ICD therapy, as well as the risks of amiodarone, may not apply to such patients. Third, although the use of distribution-based cutoff values such as tertiles is useful, the relationships in the data were continuous and do not support the rigid use of cut points. Finally, the analyses of cause-specific mortality were done in an attempt to elucidate complex relationships within our dataset. Methodologically, there is no completely satisfactory way to conduct such an analysis because of the distortions introduced between the baseline variables and causes of mortality other than the one of interest and because of the imperfections in our ability to accurately classify the cause of death, even with the assistance of a blinded clinical events committee, such as was used in this study. Our analysis used censoring to exclude deaths other than those upon which the analysis was focused. When we repeated the analyses removing patients with these other events from the dataset instead of censoring them, our results were unchanged. Note should also be made that these analyses had reduced power relative to the analyses looking at all deaths.

Conclusions

Patients with a 6MW distance of <288 m did not derive benefit from either prophylactic ICD implantation or amiodarone therapy. ICD therapy had a strongly favorable impact on survival for NYHA functional class II patients and those with a 6MW distance >288 m. Our findings further suggest harm from primary prevention amiodarone therapy in the group of heart failure patients with the lowest 6MW distance, <288 m. These results confirm and extend the previously-reported finding that ICD therapy did not benefit NYHA functional class III patients in the SCD-HeFT trial. These data should be included in shared decision-making with patients for whom they apply.

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Key Words: 6-min walk ■ amiodarone ■ congestive heart failure ■ implantable cardioverter-defibrillator ■ sudden cardiac death.

APPENDIX

For a supplemental table, please see the online version of this article.